which were targeted for Zyprexa off-label marketing, albeit less frequently than the physicians who are writing the prescriptions.

143. To identify and target the most influential doctors, Lilly encouraged LTC representatives to develop personal relationships with the LTC pharmacies to gain access to the pharmacies' local prescribing data.

144. In addition, LTC pharmacies provide consultant pharmacist services to the LTC facilities they service. Such consultant pharmacists work closely with physicians writing orders in LTC facilities to purported "educate" LTC physicians about prescription alternatives.

145. Because of the significant influence LTC pharmacies play in the prescribing decisions of LTC physicians, Plaintiff-Relator made once monthly sales calls to LTC pharmacies in her territory to ensure the pharmacies encouraged the use of Zyprexa in the facilities they service. Plaintiff-Relator specifically recalls making sales calls to LTC pharmacies to combat financially-incentivizing rebate agreements the LTC pharmacies had negotiated with Janssen, the manufacturer of Zyprexa's competitor Risperdal. Such rebate agreements made it *profitable* for the LTC pharmacy to use its consulting pharmacists power and influence to push LTC physicians to use Risperdal over Zyprexa.

146. Plaintiff-Relator and the LTC sales division generally were also instructed and trained on how to obtain Drug Utilization reports, also known by the acronym "DURs," from the LTC skilled nursing home executive staff. See Exhibit "G."

147. A "Drug Utilization Report" is a report delineating protected health information detailing which patients were taking which drugs and which physician was prescribing those drugs.

148. Lilly enforced this directive by tracking LTC sales representatives' success rates in obtaining the coveted DUR reports. See e.g. Exhibit "H."

149. To keep the LTC sales representatives across the nation abreast of Zyprexa LTC sales as well as successful LTC promotional tactics, Lilly disseminated a LTC Best Practices Newsletter 4 times a year. *Id.*

150. The LTC Best Practices Newsletter is packed with evidence and admissions of Lilly's unlawful LTC off-label marketing campaign. *Id.* It openly addresses Lilly's improper expectation that Lilly LTC sales representatives gain access to protected confidential patient information (i.e. DURs), instructs the sales representative to do rounds with the "NH [nursing home] prescriber" – a highly offensive invasion upon the doctor patient privilege, and contains messages from Lilly executives such as Grady Grant and Tom Olinski, Lilly National Sales Directors and Mike Murray – the LTC Western Division Sales Director and identifies LTC top sales performers across the nation to "SELL ZYPREXA!" The Newsletter also features a "Coaches Corner," which provides tips on maximizing LTC sales of Zyprexa. In the 2003 Winter edition of the Newsletter, the Coaches Corner featured an article by "Wayne Mielke, [the] "Long Term Care Coaching Champ of 2001, on the importance of **DUR ATTAINMENT**." *Id.*

151. Plaintiff-Relator received the quarterly Lilly LTC Best Practices Newsletter in the course and scope of her Lilly employment.

152. Lilly paid honoraria or speaker fees as part of their overall off label Zyprexa marketing scheme. The payment of and acceptance of the financial incentives in exchange for prescriptions violated the federal Anti-Kickback Statute. See § XI.

153. Lilly management approved huge speaker fee budgets as a means to disguise large payments to physicians who were willing to prescribe Zyprexa off label. Lilly established large budgets for each LTC representative to induce physicians to write off label. The speaking fees were typically $1500 for a "lunch and learn."

154. One method employed by Lilly to conceal kickback payments under the guise of legitimacy was the creation of a "speaker" program. Lilly even established an annual budget for LTC sales representatives to "invest" in speaker fees/honoraria as well as an annual entertainment budget to impress and attract physicians' business.

155. Physicians were even "groomed" by Lilly to be speakers by attending all-expense paid speaking seminars in resort-like atmospheres. These seminars were in truth designed to market Zyprexa, not to provide speaker training. For large volume prescribers,

regardless of whether they exhibited a shred of public speaking acumen, after the seminar such physicians were retained and paid handsomely to speak about Zyprexa.

156. The speaking engagements were frequently a mere sham, indeed, Plaintiff-Relator has personal knowledge that such Lilly-paid speakers were even paid to give pointless presentations to their colleagues at the healthcare facility with which they were affiliated.

157. Such thinly-veiled kickback payments were made with the intent that in return, the paid physician would prescribe Zyprexa for symptoms and illnesses that were unrelated to schizophrenia and bipolar disorder to the frail elderly population. Lilly LTC sales representatives used their improper access to DURs to identify physicians to solicit to enter into unlawful financial relationships.

158. Plaintiff-Relator has personal knowledge that Lilly established similar illegal referral relationships with health care providers throughout the United States.

159. Sales representatives, including Plaintiff-Relator, were instructed by Lilly on implementing "Peer-to-Peer Programs" intended on having paid physicians lecture on designated topics, including off-label topics. Typically, sales representatives, including Plaintiff-Relator, would organize continuing medical education ("CME") programs and offer these programs to their physician customers.

160. By way of example, one such program was "FDA Regulated Programs (Promotional)" wherein the sales representative selects a program topic and a physician under contract with Lilly Lecture Bureau. If the chosen speaker is not under contract, he or she must sign a contract to speak about Lilly's products. See Exhibit "I." The Sales representative submits a speaker payment request to Lilly's Lecture Bureau.

161. To complete the payment process to physicians, Plaintiff-Relator would contact the Lilly Lecture Bureau and the Lilly Lecture Bureau arranged for the check to be sent, typically directly to the lecturing physician. See Exhibit "J."

162. Lilly's Peer to Peer Programs Implementation Guides stresses that the "program time should be balances equally with entertainment time." See Exhibit "K."

Further, the sales representative was instructed to pre-set menus and "pre-select wine list and order group appetizers." *Id.*

163. Another example of a Lilly Peer to Peer Program is the Independent Scientific Exchange (Non promotional Program). This program is ostensibly initiated by the medical institution. The institution contacts the sales representative or Lilly Lecture Bureau directly. Then, Lilly's Lecture Bureau sends the specific institution their "grant request letter." See Exhibit "L." The grant request may contain a request for an honorarium to speak, as well as a request for food, beverages, travel and other expenses. LLB sends grant checks to the institution or physician within 7 days after completion of the program, and sometimes prior to the program. *Id.*

164. Further, by way of example, sales representatives could also initiate "Customer Entertainment" as a Peer to Peer Program. The sales representative invites customer physicians to specific events (i.e., sporting events, concerts, theater or dinners). If the incentive of choice was a dinner, the sales representatives were instructed to select the best items on the menu and select a red and white wine for the table." See Exhibit "M "

165. Lilly's routine practice of paying kickbacks was intended to and did amplify physicians' off-label overutilization of Zyprexa for their patients.

166. Lilly knew that the payments constituted kickbacks in reckless disregard of the law. Lilly was also acutely aware that the safe harbors established by the HHS did not cover the exorbitant payments being made. Lilly intended these payments to encourage Zyprexa overutilization in off-label demographics.

2) Illegal Off-Label Marketing to Primary Care Physicians

167. Lilly's national off-label Zyprexa marketing campaign targeting primary care physicians ("PCPs") was designed to make Zyprexa part of the everyday prescribing habits of not only LTC physicians treating the elderly, but also PCPs in their office practices.

168. In order to grow Zyprexa market share sales and surpass competing antipsychotics such as Risperdal, Lilly undertook a scheme to market and promote Zyprexa

for off-label purposes beyond LTC, Lilly concomitantly launched a marketing campaign targeting PCPs. The campaign was designed to "educate" PCPs about which patients they regularly see in their practices who present with symptoms treatable with Zyprexa, *i.e.*, albeit off-label use. Lilly's goal being to make Zyprexa the cornerstone of PCPs everyday prescribing habits.

169. Similar to the LTC sales message, Lilly's PCP off-label Zyprexa promotional campaign focused on symptoms, not diagnoses. To achieve this goal, Lilly PCP sales representatives were trained to deliver a Zyprexa marketing message that centered on symptoms associated with mood, thought, and behavioral disturbances.

170. Lilly targeted PCPs because of the fundamental role PCPs play in patient care and in prescribing drugs to treat a multitude of symptoms, thereby maximize profits and growing market share. In addition, Lilly marketed Zyprexa to primary care physicians for non-indicated uses, because Lilly's marketing studies demonstrated that PCPs generally had less awareness of Lilly's indicated uses and treatment-emergent side effects. Lilly sales material encouraged representatives to promote Zyprexa as a "safe, gentle psychotropic" suitable for people with mood-related symptoms.

171. Lilly PCP sales representatives were trained and instructed to market Zyprexa to PCPs by suggesting that there were a plethora of patients in the physician's practice exhibiting "irritability," "disruptive behavior," "poor sleep," "elevated mood," "depressed mood," "anxiety" and "irregular sleep patterns" and that Zyprexa is a safe and efficacious drug to treat such symptoms.

172. Just as it did for the LTC sales force, Lilly created several promotional caricatures tailored to market Zyprexa to PCPs. The primary PCP caricature Plaintiff-Relator became familiar with is "Donna." "Donna" is a mother of two children in her early 30's who is distracted and depressed and these symptoms are interfering with her daily life. Perhaps Donna has been prescribed drugs that treat depression. Lilly sales representatives were trained and instructed to encourage PCPs with "Donnas" in their practice to prescribe Zyprexa, although she has not been diagnosed with either bipolar mania or schizophrenia.

173. Lilly developed Donna knowing that millions of people fit Donna's broadly defined profile and who are not psychotic, schizophrenic, or bipolar. This way, Lilly could accomplish its primary goal to drive off-label sales of Zyprexa by causing as many unsuspecting adult patients on Zyprexa as possible.

174. Plaintiff-Relator has personal knowledge that Lilly's promotion of Zyprexa to PCPs, including her presence in PCP physicians' offices during a Lilly PCP sales representative's sales call.

175. Each LTC sales representative's territory "overlapped" with a Zyprexa PCP sales representative. Lilly expected its LTC representatives to coordinate with his or her overlap.

176. Accordingly, Plaintiff-Relator periodically made joint sales calls to PCPs who also treated LTC residents with her "overlap." During these joint Zyprexa sales calls, Plaintiff-Relator witnessed her Lilly PCP overlap deliver the Zyprexa off-label PCP marketing message designed to promote Zyprexa's superior efficacy and safety for treating adult patients who presented with symptoms relating to mood, anxiety, and depression, while omitting that Zyprexa is not indicated for the treatment of such symptoms not attendant to the diagnosis of bipolar disorder or schizophrenia.

177. Plaintiff-Relator witnessed the PCP overlap use, wherein the PCP sales representatives referred and relied upon the Donna profile to promote Zyprexa off-label for depression and mood disorders. At no time did the PCP sales representative initiate any discussion about Zyprexa's lack of indication for the treatment of such symptoms in patients not diagnosed with schizophrenia or bi-polar disorder.

178. Lilly's efforts to promote Zyprexa for use as a general mood stabilizer in the treatment of depression have resulted in billions of dollars of revenue for the company.

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X. LILLY CAUSED THE SUBMISSION OF FALSE CLAIMS FOR ZYPREXA REIMBURSEMENT TO BE SUBMITTED BY LONG TERM CARE PHARMACIES

A. Zyprexa Prescribed Off-label to LTC Residents Was Ineligible for Reimbursement by the Medicaid Program

179. Prior to the enactment of the Medicare Part D program, Medicaid purchased an estimated 80-90% of atypical antipsychotic prescriptions. Of the top 30 drugs by total US revenue, Zyprexa is the most expensive. As detailed herein, the FDA defines off-label use as indications, dosage, form, dose regimen, population or other use parameter not mentioned in the approved labeling.

180. Because prescriptions for off-label uses generally are not eligible for reimbursement, under Medicaid and Medicare regulations, submission of a claim for reimbursement for a drug prescribed off-label constitutes a false claim for the purposes of the State of California's False Claims Act. While it is a pharmacy, by virtue of the reimbursement system, which unwittingly submits the false prescription drug claim, the person or persons who knowingly cause(s) such a claim to be presented to the State of California, including the State of California, is liable under the law. Here, Lilly's California False Claims Act violations arise from its successful attempts to induce LTC pharmacies to unwittingly defraud the State of California.

181. Lilly knew that medically unnecessary, off-label Zyprexa prescriptions were ineligible for Medicaid reimbursement and that its activities would, in fact, cause numerous ineligible prescriptions to be submitted to Medicaid and Medicare by the LTC pharmacies which arranged for pharmaceutical benefits to LTC patients.

182. The unwitting participation of the LTC pharmacies in the submission of false claims was not only foreseeable; it was an intended consequence of Lilly's scheme of fraud.

183. Absent Lilly's intentional, illegal off-label marketing in the LTC demographic, and its unlawful financial relationships with doctors, Zyprexa would not have been prescribed off-label. Lilly's off-label marketing programs have been extremely

successful, leading to the submission of claims to the Medicare and Medicaid programs for medically unnecessary and imprudent prescriptions which otherwise would not have been paid by Medicare and Medicaid.

184. Each Zyprexa claim submitted to the State of California for Zyprexa prescribed for an off-label use not only violates Medicare payment rules, but constitutes the submission of a fraudulent claim redressable by California's False Claims Act, Cal. Gov. Code §§ 12650 et seq.

185. The remedial provisions of the California's False Claims Act is the necessary vehicle to obtain redress for the substantial economic harm suffered by Medi-Cal as a result of the millions of dollars of Zyprexa reimbursement claims caused to be written and submitted by enrolled Medi-Cal pharmacy benefits providers to the State of California as a direct and foreseeable result of Lilly's illegal off-label marketing campaign.

186. Lilly's wanton misconduct has been ongoing since at least 2001.

XI. THE CALIFORNIA FALSE CLAIMS ACT

187. The California False Claims Act, Cal. Gov. Code §§12650 et seq., provides, in pertinent part that a person is liable to the State of California for a civil penalty of up to $10,000, plus not less than two times and not more than three times the amount of damages which the State of California sustains because that person, *inter alia*,:

(a) Liability for certain acts. Any person who—

(1) Knowingly presents, or causes to be presented, to an officer of the state or of any political subdivision thereof, a false claim for payment or approval;

(2) Knowingly makes, uses, or causes to be made or used, a false record or statement to get a false or fraudulent claim paid or approved by the state or by any political subdivision;

(3) Conspires to defraud the state or any political subdivision by getting a false claim allowed or paid by the state or by any political subdivision;

(4) Has possession, custody, or control of public property or money used or to be used by the state or by any political subdivision and knowingly delivers or causes to be delivered less property than the amount for which the person receives a certificate or receipt;

(5) Is authorized to make or deliver a document certifying receipt of property used or to be used by the state or by any political subdivision and knowingly makes or delivers a receipt that falsely represents the property used or to be used;

(6) Knowingly buys, or receives as a pledge of an obligation or debt, public property from any person who lawfully may not sell or pledge the property;

(7) Knowingly makes, uses, or causes to be made or used a false record or statement to conceal, avoid, or decrease an obligation to pay or transmit money or property to the state or to any political subdivision; or

(8) Is a beneficiary of an inadvertent submission of a false claim to the state or a political subdivision, subsequently discovers the falsity of the claim, and fails to disclose the false claim to the state or the political subdivision within a reasonable time after discovery of the false claim.

188. Under § 12650(b) (1) – (3) of California's False Claims Act, "Knowing" and "knowingly" mean that a person, with respect to information, does any of the following: (1) Has actual knowledge of the information, (2) Acts in deliberate ignorance of the truth or falsity of the information or (3) Acts in reckless disregard of the truth or falsity of the information. Proof of specific intent to defraud is not required.

XII. DEFENDANT LILLY'S VIOLATIONS OF THE FEDERAL AND CALIFORNIA ANTI-KICKBACK STATUTES CAUSED FALSE CLAIMS TO BE SUBMITTED TO THE GOVERNMENT

A. Federal Anti-Kickback Statute Prohibitions

192. The Medicare and Medicaid Fraud and Abuse Statute (Statute) was first

enacted under the Social Security Act in 1977. The Statute imposes criminal penalties on whomever violates the Anti-Kickback Provision and states in relevant part, whoever knowingly and willfully offers or pays remuneration (including any kickback, bribe or rebate) directly or indirectly, overtly or covertly, in cash or in kind to any person to induce such person:

> (A) to refer an individual to a person for the furnishing of or arranging for the furnishing of any item or service for which payment may be made in whole or in part under a Federal health care program, or
>
> (B) to purchase or lease, order or arrange for or recommend purchasing, leasing, or ordering any good, facility, service or item for which payment may be made in whole or in part under a Federal Health care program.

42 U.S.C. § 1320a-7b(b)(2)(A) & (B).

193. By its terms, the Federal Medicare and Medicaid Anti-Kickback Statute prohibits certain conduct involving improper payments in connection with the delivery of goods or services, including prescription drugs, covered by Medicare, Medicaid and other federal health care programs.

194. Illegal payments or solicitations of payments include those in cash or in kind, *i.e.*, goods, those made directly or indirectly, and those made overtly or covertly.

195. A violation of the AKS arises if *one purpose* of the payment was to induce future referrals even if the payment was also intended to compensate for professional services. *United States v. Kats*, 871 F.2d 105 (9th Cir. 1989).

196. Such illegal inducement relationships between drug companies and physicians endanger patients and harm the State of California because, as is alleged herein, they encourage unnecessary treatments, contaminate the free exercise of medical judgment by physicians, limit patient options and lead to higher federal and state payments for prescription drug benefits. The Anti-Kickback Statute was promulgated to thwart such dangerous practice of medicine.

197. The remuneration paid by Lilly and accepted by participating Med-Cal

physicians all across the country, as alleged in detail *supra*, fit squarely within the AKS's definition of illegal remuneration.

198. As alleged herein, in violation of the AKS, Lilly paid, and physicians accepted, unlawful remuneration, including cash payments thinly-veiled as "speaker fees," honoraria, unrestricted educational grants and other gratuities as *quid pro quo* for volume prescription writing of Zyprexa to LTC patients, children and adults, notwithstanding Lilly's knowledge of the prohibitions of offering, paying or receiving items of value in exchange for arranging the purchase of any good paid for in whole or in part by the federal government.

199. Lilly entered into unlawful inducement relationships in violation of the Anti-Kickback Statute with LTC physicians, PCPs, pediatric physicians and other medical professionals nationwide.

200. Although "safe harbor" regulations exist to protect certain relatively innocuous and even beneficial commercial arrangements, no such provision protects the kickbacks paid by Lilly.

201. Lilly prevented the State of California from knowing of the underlying violations of the federal and California AKS violations by concealing its illegal agreements with Medi-Cal participating providers as well as concealing the exchange of illegal remuneration pursuant thereto.

B. Violations of California's Health & Safety Comprehensive Compliance Program

202. California's Health and Safety Code §§ 119400-119402 relates to prescription drug and medical device marketing practices. The California Marketing Compliance Law ("CMCL") requires pharmaceutical companies and medical device manufacturers to adopt Comprehensive Compliance Programs (CCPs) that meet the standards set forth in the compliance guidance for pharmaceutical companies published by the Department of Health and Human Services' Office of Inspector General (OIG). CA Health & Safety Code §119400(a). These compliance programs must also contain provisions concerning their interactions with medical and health professionals, and adopt limits on gifts to such

professionals. Finally, the CMCL requires covered companies to make certain compliance declarations publicly. California Health and Safety Code §§ 119400-119402.

203. The CMCL applies to entities "engaged in the production, preparation, propagation, compounding, conversion, or processing of dangerous drugs, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical synthesis or by a combination of extraction and clinical synthesis." California Health and Safety Code § 119400(c). The law also states that "pharmaceutical company" also means "an entity engaged in the packaging, repackaging, labeling, re-labeling, or distribution of dangerous drugs," as well as "a person who engages in pharmaceutical detailing, promotional activities, or other marketing of a dangerous drug in ... [California] on behalf of a pharmaceutical company." California Health and Safety Code § 119400(c).

204. The CMCL also regulates interactions by drug and device companies with "medical or health professionals," which are defined as persons licensed by state law to prescribe drugs for human patients, a medical student, or a drug formulary committee member. California Health and Safety Code § 119400(b).

205. Drug and device manufacturers must adopt a Comprehensive Compliance Program that is "in accordance with" the Office of Inspector General's 2003 Compliance Program Guidance for Pharmaceutical Manufacturers. California Health and Safety Code § 119402(a).

206. The CMCL requires manufacturers to implement "a specific annual dollar limit on gifts, promotional materials, or items or activities" that the manufacturer may provide to medical or health care professionals, in accordance with the OIG Compliance Guidance and the Pharmaceutical Research and Manufacturers of America in July 2002 (the PhRMA Code). California Health and Safety Code § 119402(c)-(d).

207. The CMCL requires that manufacturers "annually declare" in writing that they are in compliance with their own CCP and with the CMCL. California Health and Safety Code § 119402(e).

208. By its terms, the California's Health and Safety Code §§ 119400-119402

prohibits certain conduct involving improper payments in connection with the delivery of goods or services, including prescription drugs, covered by Medicare, Medicaid and other federal health care programs.

194. Illegal payments or solicitations of payments include those in cash or in kind, *i.e.*, goods, those made directly or indirectly, and those made overtly or covertly.

195. Such illegal inducement relationships between drug companies and physicians endanger patients and harm the State of California because, as here, they encourage unnecessary treatments, contaminate the free exercise of medical judgment by providers, limit patient options and lead to higher federal and state payments for prescription drug benefits. California's Health and Safety Code §§ 119400-119402 was promulgated to thwart such dangerous practice of medicine.

197. The remuneration paid by Lilly and accepted by physicians all across the country, including the State of California, as alleged in detail *supra*, are precisely the type of conduct California's Health and Safety Code §§ 119400-119402 aims to prohibit.

198. As alleged herein, in violation of California's Health and Safety Code §§ 119400-119402, Lilly paid, and physicians accepted, unlawful remuneration, including cash payments thinly-veiled as "speaker fees," honoraria, unrestricted educational grants and other gratuities as *quid pro quo* for volume prescription writing of Zyprexa to LTC patients, children and adults, notwithstanding Lilly's knowledge of the prohibitions of offering, paying or receiving items of value in exchange for arranging the purchase of any good paid for in whole or in part by the federal government and the State of California.

199. Lilly entered into unlawful inducement relationships in violation of California's Health and Safety Code §§ 119400-119402 with LTC physicians, PCPs, pediatric physicians and other medical professionals nationwide.

200. Although "safe harbor" regulations exist to protect certain relatively innocuous and even beneficial commercial arrangements, no such provision protects the kickbacks paid by Lilly.

201. Lilly prevented the State of California from knowing of California's Health

and Safety Code §§ 119400-119402 violations by concealing such agreements.

C. Defendant Lilly's Anti-Kickback Statute Violations and Violations of California's Health and Safety Code §§ 119400-119402 are Predicate Acts Giving Rise to Liability Under the State and Federal False Claim Acts

202. The Anti-Kickback Statute and California's Health and Safety Code §§ 119400-119402 work hand in glove with the False Claims Act. As a matter of law, violations of the AKS and California's Health and Safety Code §§ 119400-119402 state a cause of action under the False Claims Act. Indeed, compliance with the AKS, as well as all other relevant laws and regulations, is a condition of payment by Medicaid for prescription drug claims. 42 U.S.C. §1320a-7b(b).

203. Thus, where conduct that violates the Anti-Kickback Act or California's Health and Safety Code §§ 119400-119402 results in goods and services (here, Zyprexa) provided to Medi-Cal beneficiaries, that good or service is *ineligible* for reimbursement under Medi-Cal payment rules and federal law.

204. Thus, as a matter of law, prescription drugs and other products purchased in violation of the AKS or California's Health and Safety Code §§ 119400-119402 are ineligible for Medi-Cal reimbursement. By and through the covert payment of illegal kickbacks, Lilly defrauded, *inter alia*, Medi-Cal -participating pharmacies into presenting reimbursement claims for Zyprexa to the State of California containing the false certification that the claim was submitted in compliance with the AKS or California's Health and Safety Code §§ 119400-119402 and other applicable regulations.

205. The State of California would appropriately have denied Zyprexa reimbursement claims if it had knowledge that the Zyprexa prescription written which gave rise to the claim for reimbursement was the product of an illegal kickback arrangement.

206. Defendant Lilly, acting in concert with physicians, caused, *inter alia*, Medicaid-participating pharmacies all across the country to submit claims that were rendered ineligible for reimbursement by Lilly's violations of the AKS and California's Health and Safety Code §§ 119400-119402 as well as caused such pharmacies to explicitly falsely certify

that they were acting in compliance with all applicable laws and regulations, including the AKS, for each and every claim the pharmacies submitted. The pharmacies' certifications Lilly caused to be submitted to the State of California, however, were false when made.

207. Such pharmacies reasonably and justifiably relied upon the validity and medical appropriateness of the Zyprexa prescriptions.

208. Lilly's illegal scheme had one intended purpose and result – increasing Zyprexa profits – and therefore certified claims for Zyprexa prescriptions instead of cheaper alternatives were submitted to the State of California for payment by pharmacies throughout the nation. Accordingly, at all times relevant to the Complaint, Lilly acted with the requisite scienter.

209. The result of the Lilly's scheme was a dramatic increase in the number of claims submitted to the State of California for the higher priced Zyprexa, which led to dramatically higher revenue for Lilly. Lilly's increased revenues, and the correspondingly-increased cost to the Government healthcare programs, were the direct, intended, and foreseeable result of the unlawful kickbacks payments made by Lilly to LTC physicians, PCPs and pediatric physicians.

210. Lilly's liability under §§ 3729(a)(1) and (a)(2) of the Federal False Claims Act, §§ 68.082(a) and California False Claims Act, Cal. Govt. Code §12650 *et seq*. arises from the drug company's overt and willful participation in causing the basis for false claims to be made through the establishment of an illegal and corrupt financial relationships.

211. Lilly's conduct is also punishable under §12651 (a)(3) of the Federal False Claims Act, and California False Claims Act, Cal. Govt. Code §12650 *et seq*., for entering into an unlawful conspiracies with the intent to defraud the Government.

FIRST CAUSE OF ACTION
California False Claims Act
Ca. Government Code §12650 *et seq*.

212. Plaintiffs reallege and incorporate by reference all of the foregoing paragraphs as if fully set forth herein.

213. This Count is brought by Plaintiff-Relator Vicente in the name of the State of California under the *qui tam* provisions of the California False Claims Act, California Government Code §12651(a).

214. Defendant Lilly at all times relevant to this action sold and marketed, and continues to sell and market, pharmaceuticals, including Zyprexa, in the State of California.

215. A significant percentage of patients who use or have been prescribed Zyprexa off-label for non-medically necessary uses as a result of Lilly's unlawful off-label marketing campaign are persons whose prescriptions are paid for in whole or in part by Medi-Cal or other State funded healthcare programs.

216. At all times relevant and material to this Complaint, Lilly has induced a misallocation of California's funds through a pattern of fraudulent conduct, as alleged herein. Lilly intentionally concealed its campaign to market Zyprexa in California and throughout the United States for un-approved indications and medically unnecessary uses for the purpose of, and with the effect of, unlawfully increasing purchases of Zyprexa prescriptions by Medi-Cal that would not have funded but for Lilly's active concealment of its unlawful Zyprexa off-label marketing campaign.

217. By the conduct alleged in this Complaint, Lilly has knowingly and foreseeably caused the submission false claims for payment or approval that Lilly knew to be ineligible for reimbursement and the cost of which would be borne by California by and through, *inter alia,* Medi-Cal, to be presented to officers and employees of the State of California. Defendant has also caused false records and statements to be submitted to officers and employees of the State of California to get its false claims paid.

218. Lilly's conduct includes its deceptive and illegal scheme to expand off-label use of Zyprexa by, *inter alia*, 1) marketing Zyprexa in a misleading and/or disingenuous way for off-label uses and populations to physicians in the long term care and primary care markets and 2) orchestrating a kickback scheme pursuant to which, in sum, it paid physicians in cash and in kind in exchange for writing off-label prescriptions of Zyprexa. As a result, the California has paid false claims submitted for the Zyprexa drugs by Medi-

Cal participating pharmacies, resulting in great financial loss to the State.

219. Lilly's conduct constitutes the intentional violation of the California False Claims Act and other laws.

220. The claims for Zyprexa caused to be submitted by Lilly constitute false claims because, *inter alia*, Medi-Cal reimbursement is not available for non-medically accepted indications or non-medically necessary uses of prescription drugs as alleged herein.

221. By virtue of the above-described acts, Lilly has also knowingly and intentionally conspired to, and caused false claims for payment to be submitted for Zyprexa from the implementation of its kickback scheme as well as caused false records and statements to be submitted to get false Zyprexa claims paid. Lilly's kickback scheme violated the Federal Anti-Kickback Statute and the analogous law of the State of California and has thereby caused the submission of false claims and records to Medi-Cal.

222. It was the intended and foreseeable effect of Lilly's kickback scheme to cause pharmacies to routinely submit thousands false claims requesting reimbursement for expensive Zyprexa prescriptions.

223. The amounts of the false or fraudulent claims and records or statements caused by Lilly to be submitted to Medi-Cal were material.

224. Plaintiff California, being unaware of the falsity of the claims and statements or records caused to be made by Defendant Lilly as alleged herein, and in reliance on the accuracy thereof, paid and may continue to pay for off-label prescriptions of Zyprexa.

225. All unlawful conduct described above may have continued after Plaintiff-Relator's voluntary decision to seek alternative employment.

226. By reason of the conduct described above, California has been damaged in an amount that is believed to be in excess of tens of millions of dollars annually for claims submitted for Zyprexa in Northern California alone.

227. California is entitled to multiple damages under the California False Claims Act, to be determined at trial, plus a civil penalty of up to $10,000 for each ineligible claim

submitted to Medi-Cal for payment.

SECOND CAUSE OF ACTION

Conspiracy to Submit False Claims in Violation of the California False Claims Act Ca. Gov't Code §12651(a)(3)

228. Plaintiffs re-allege and incorporate by reference all of the foregoing paragraphs as if fully set forth herein.

229. By entering into illegal kickback agreements as detailed herein, Defendant Lilly conspired with healthcare providers to defraud the State of California causing the submission of false claims for Zyprexa. At all times relevant to the complaint, Defendant Lilly knowingly violated the Anti-Kickback Statute.

230. As a result of the claims for reimbursement Defendant Lilly caused to be submitted to Medi-Cal, which were falsely certified compliant with federal and state Medicaid law and regulation as a condition of payment to LTC pharmacy benefit providers, California regularly made payments to pharmacies for Zyprexa.

231. The amounts of the false or fraudulent claims to the State of California were material.

232. Plaintiff State of California, being unaware of the falsity of the claims and/or statements made by Defendant Lilly, and in reliance on the accuracy thereof paid and may continue to pay for Zyprexa. All unlawful conduct described above may have continued after Plaintiff-Relator voluntary left Lilly's employ.

233. The State of California is entitled to multiple damages under the California False Claims Act, to be determined at trial, plus a civil penalty of up to $10,000 for each ineligible claim submitted to Medi-Cal for payment.

THIRD CAUSE OF ACTION

(Violation of Business & Profession Code § 17200)

234. Plaintiffs re-allege and incorporate by reference all of the foregoing paragraphs as if fully set forth herein.

235. Plaintiffs are informed and believe and allege that Lilly, by the acts and misconduct alleged herein, violated Business and Professions Code sections 17200.

236. California Business & Professions Code Section 17200 provides that unfair competition shall mean and include "all unlawful, unfair or fraudulent business practices and unfair, deceptive, untrue or misleading advertising."

237. The acts and practices described herein were and are likely to mislead the general public and therefore constitute unfair business practices within the meaning of Business & Professions Code Section 17200. The acts and untrue and misleading advertising set forth in presiding paragraphs are incorporated by reference and are, by definition, violations of Business & Professions Code Section 17200. This conduct includes, but is not limited to:

a. Representing to the State of California and the general public that Zyprexa was safe, fit and effective for human consumption, knowing that said representations were false, and concealing from the State of California and the general public that Zyprexa has a serious propensity to cause injuries to users;

b. Engaging in advertising programs designed to create the image, impression and belief by consumers, physicians and others that the use of Zyprexa was safe for human use, had fewer side effects and adverse reactions than other methods for treating schizophrenia and bi-polar disorder, constituted a convenient, safe form for treating schizophrenia and bi-polar disorder, even though the Defendant Lilly knew these to be false, and even though the Defendant Lilly had no reasonable grounds to believe them to be true;

c. Purposely downplaying and understating the health hazards and risks associated with Zyprexa; and

d. Issuing promotional literature deceiving potential users of Zyprexa by relaying positive information and manipulating statistics to

suggest widespread acceptability, while downplaying the known adverse and serious health effects and concealing material relevant information regarding the safety of Zyprexa.

238. These practices constitute unlawful, unfair and fraudulent business acts or practices, within the meaning of California Business & Professions Code Section 17200, as well as unfair, deceptive, untrue and misleading advertising as prohibited by California Business & Professions Code Section 17500, as set forth herein.

239. The unlawful, unfair and fraudulent business practices of Defendant Lilly described above present a continuing threat to members of the public in that Defendant Lilly continues to engage in the conduct described therein.

240. As a result of their conduct described above, Defendant Lilly has been unjustly enriched. Specifically, Defendant Lilly has been unjustly enriched by receipt of billions of dollars in ill-gotten gains from the sale and prescription of Zyprexa in California, and other states, sold in large part as a result of the acts and omissions described herein.

241. Because of the fraudulent misrepresentations made by Defendant Lilly as detailed above, and the inherently unfair practice of committing a fraud against the State of California and the general public by intentionally misrepresenting and concealing material information, the acts of Defendant Lilly described herein constitute unfair or fraudulent business practices.

242. Plaintiffs, the State of California and Plaintiff-Relator, pursuant to California Business & Professions Code Section 17203, seek an order of this court compelling the Defendant Lilly to provide restitution, and to disgorge the monies collected and profits realized by Defendant Lilly, as a result of their unfair business practices.

243. Defendant Lilly's acts were willful, wanton, reckless and fraudulent; hence, the State of California and Plaintiff-Relator are entitled to exemplary damages, inter alia.

WHEREFORE, Plaintiffs demand judgment against Defendants and seek compensatory damages, disgorgement, restitution, and exemplary and punitive damages together with interest, the costs of suit, attorneys' fees and such other and future relief as

the Court deems just and proper.

FOURTH CAUSE OF ACTION

(Violation of Business & Profession Code § 17500)

244. Plaintiffs re-allege and incorporate by reference all of the foregoing paragraphs as if fully set forth herein.

245. Plaintiffs are informed and believe and thereon allege that Defendants, by the acts and misconduct alleged herein, violated Business & Professions Code Section 17500.

246. Plaintiffs hereby seek restitution, as well as and punitive damages against Defendant Lilly for their violations of section 17500.

247. California Business & Professions Code section 17500 provides that it is unlawful for any person, firm, corporation or association to dispose of property or perform services, or to induce the public to enter into any obligation relating thereto, through the use of untrue or misleading statements.

248. At all times herein mentioned, Defendant Lilly has committed the acts of disseminating untrue and misleading statements as defined by Business & Professions Code Section 17500 by engaging in the following acts and practices with intent to induce members of the public to purchase and use Zyprexa:

a. Representing to the State of California and the general public that Zyprexa was safe, fit and effective for human consumption, knowing that said representations were false, and concealing from the State of California and the general public that Zyprexa has a serious propensity to cause injuries to users;

b. Engaging in advertising programs designed to create the image, impression and belief by consumers, physicians and others that the use of Zyprexa was safe for human use, had fewer side effects and adverse reactions than other methods for treating mental illness, constituted a convenient, safe form for treating mental illness, even though the Defendant

Lilly knew these to be false, and even though the Defendant Lilly had no reasonable grounds to believe them to be true;

c. Purposely downplaying and understating the health hazards and risks associated with Zyprexa; and

d. Issuing promotional literature deceiving potential users of Zyprexa by relaying positive information and manipulating statistics to suggest widespread acceptability, while downplaying the known adverse and serious health effects and concealing material relevant information regarding the safety of Zyprexa.

249. The foregoing practices constitute false and misleading advertising within the meaning of California Business & Professions Code Section 17500.

250. As a result of its false and misleading statements described above, Defendant Lilly has been and will be unjustly enriched. Specifically, Defendant Lilly has been unjustly enriched by receipt of billions of dollars from the sale and prescription of Zyprexa in California and other states, sold in large part as a result of the false or misleading statements described herein.

251. Pursuant to California Business & Professions Code Section 17535, Plaintiffs seek an order of this court compelling Defendant Lilly to provide restitution, and to disgorge the monies collected and profits realized by Defendant Lilly, as a result of their unfair business practices, and injunctive relief calling for Defendant Lilly to cease such unfair business practices in the future.

JURY DEMAND

443. Plaintiffs demand trial by jury on all claims.

WHEREFORE, Relator-Plaintiff, on behalf of herself, and the State of California and the State of California, requests the following relief:

(a) Judgment against Defendant Lilly in the amount of three (3) times the amount of damages the State of California has sustained because of Defendant Lilly's actions, plus a civil penalty of $10,000.00 for each action in violation California False

Claims Act, Cal. Gov. Code §§ 12650 et seq., and the appropriate fines and penalties for violating the protective California laws applicable to the fraudulent and false conduct and the cost of this action with interest;

(b) That Plaintiff-Relator be awarded the maximum amount allowed pursuant to the California False Claims Act, Cal. Gov. Code §12651(a), plus interest, and all relief to which she is entitled pursuant to said laws;

(c) That the Plaintiff-Relator be awarded all costs incurred, including reasonable attorneys' fees;

(d) In the event that the State of California proceed with this action, Plaintiff-Relator Vicente, be awarded an appropriate amount for disclosing evidence or information that the State of California did not possess when this action was brought to the government. The appropriate amount is not greater than twenty-five percent (25%) of the proceeds of the action or settlement of a claim. The amount awarded to Plaintiff-Relator also includes the results of government actions or settlement of claims resulting from the expansion of claims through the government's further investigation directly generated from or attributable to Plaintiff-Relator's information; and,

(e) Such other relief as this Court deems just and appropriate.

DATED: May 11, 2007.

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EXHIBIT A

Why is Lilly expanding its Long Term Care Business?

- To improve care & maximize Zyprexa & Prozac sales for residents who receive their medications via a LTC pharmacy
- To build a LTC business that is the industry model which will:
  - Maximize Lilly's rich pipeline of future products
  - Attract external products to Lilly which will enhance our rich pipeline

The Golden Opportunity in Long Term Care

- One of the fastest growing segments of the US population
  - Mental disorders are common
  - Use a lot of prescription drugs

  Many of Lilly's current & future products address the unmet medical needs of LTC patients (i.e. mental disorders, diabetes/complications, osteoporosis, urinary incontinence, etc.)
- According to market research, over 50% of all residents are prescribed some type of psychoactive medicine
- Building a LTC business that is the industry model may attract external product partnerships

PAGE 3 OF
EXHIBIT A TO
COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

Mike Murray
Q1 Expectations for LTC - W

- Selling to Existing Customers (Continue Current Momentum)
  - Seamless Transfer of Information Between Representatives
  - Impeccable Customer/ Product & Disease Knowledge
  - Ability to Deliver Core Messages
  - Ability to Create Action
- Develop Deep Understanding of LTC Network in Each DGA
- Identify Key Influencers and Maximize Selling Opportunities in LTC Network

PAGE 5 OF
EXHIBIT A TO
COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

Putting the LTC Puzzle Together

LTC Pharmacies

Pharmacists that drive 80% of $ - Confirm #/open/closed

Nursing Homes supplied	Key Writers
$ Opportunity	Consultant RPh's
$ Lilly AD/AP	In Service Needs
$ Competitive	MIQ
	- Psychotropic DUR

Nursing Home
Psychotropic DUR
Key prescribers/influencers (Med. Dir.)

Key Providers (Physicians)
- Sell them
- Who are they
- What are they using
- Why are they using it
- How many
- Best times to see office / NH
  - Nurse Practitioner
  - PA
- Geriatric psych they work with

Director of Nursing
- Sell them
- In service needs
- MIQ
  - Psychotropic DUR
  - QA Meetings

Consulting Pharmacists
- Sell them
- Interventions in place
- In service needs
- Pull thru opportunities

Goal - Basics in Place - SELL

Targets - 80 to 110 key physicians/territory
- 15-20 gold

Frequency - routing schedule to drive 6-8 calls/day
- Whales 2x's month/everyone else 1x month

Message - physician knowledge to drive pre-call plan
- Negotiate for new business
- ARP note on every call

Resource Utilization - Peer-to-Peer
- Build around whales

Brand Team Support

EXHIBIT B

Dear Doctor,

This resident is receiving Zyprexa 2.5 mg daily at ____ am/pm. Current geriatric studies demonstrate that Zyprexa provides superior efficacy and safety when compared to placebo and significantly reduced caregiver burden at a dose of 5mg daily[1]. Zyprexa has also demonstrated superior efficacy in treating active, passive, and verbal aggression, as well as hallucinations and delusions[2]. Please consider upgrading this resident's treatment to 5mg daily at 5 p.m. to optimize their therapy.

---

[1] Street JS, Clark WS, Gannon KS, et al. 2000. Olanzapine treatment of psychotic and behavioral symptoms n patients with Alzheimer's disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 57:968-976.
[2] Edell et al

Dear Doctor,

This resident is receiving Zyprexa ___ mg ___(QD, BID) at ____ am/pm and either has difficulty swallowing or has a G-tube. Zyprexa Zydis is a new formulation of Zyprexa that is an orally disintegrating tablet that can be placed on the resident's tongue or dissolved in water to be administered via G-tube. Please consider upgrading this resident's therapy to Zyprexa Zydis___ mg ___(QD, BID) at ____ am/pm to reduce the nursing time and effort required to administer this resident's medication therapy.

EXHIBIT C TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT D TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT E TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT F TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT G TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT H TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT I TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT J TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT K TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT L TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT M TO COMPLAINT FOR DAMAGES

DOCUMENT SUBMITTED UNDER SEAL

EXHIBIT N

ARCHIVES OF GENERAL PSYCHIATRY

October 2000

Olanzapine Treatment of Psychotic and Behavioral Symptoms in Patients With Alzheimer Disease in Nursing Care Facilities

A Double-blind, Randomized, Placebo-Controlled Trial

J. S. Street, W. S. Clark, K. S. Gannon, J. L. Cummings, F. P. Bymaster, R. N. Tamura, S. J. Mitan, D. L. Kadam, T. M. Sanger, P. D. Feldman, G. D. Tollefson, A. Breier, for the HGEU Study Group

American Medical Association
Physicians dedicated to the health of America

Important Information for Readers Provided by Eli Lilly and Company

The attached reprint discusses safety, efficacy and other information about Zyprexa® (olanzapine) which may be different from the information contained in the approved full prescribing information.

INDICATIONS AND USAGE: Zyprexa is indicated for the short-term treatment of schizophrenia and for the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

The attached article describes the results from a double-blind, placebo-controlled trial designed to examine the safety and efficacy of Zyprexa in elderly patients exhibiting psychotic and/or behavioral symptoms in association with Alzheimer's disease. The study methodology and design are described in this article. The following are important considerations for the reader:

This reprint discusses the use of olanzapine for the treatment of elderly patients with psychotic features related to Alzheimer's disease. The full prescribing information for Zyprexa does not reflect specific efficacy data for this population. The full prescribing information states that studies have suggested there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Two olanzapine-treated patients (2/407) in 2 studies in patients with Alzheimer's disease died from aspiration pneumonia during or within 30 days of the termination of the double-blind portion of their respective studies; there were no deaths in the placebo-treated patients. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia.

The efficacy measures for this study were based on the Neuropsychiatric Inventory/Nursing Home Version (NPI/NH), including the effects of individual symptom items relative to occupational disruptiveness and job satisfaction for the caregiver staff. These measurements are not reflected in the prescribing information for Zyprexa.

This reprint discusses adverse event and other data from the study reported which may not be consistent with the overall trial database or postmarketing experience with Zyprexa. While safety information from this study is included in the full prescribing information for Zyprexa, the prescribing information may also reflect additional or different information based on a safety database comprised of a number of Lilly clinical studies and postmarketing reports (a copy of the full prescribing information is attached).

This reprint discusses the receptor binding profile of Zyprexa and the relationship between receptor binding and certain observed side effects. The authors note that while olanzapine demonstrates a relatively high affinity in vitro for muscarinic receptors, it appears to have relatively minimal functional effects at these receptors. The full prescribing information states that olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic effects.

The authors comment on a number of studies in elderly demented patients involving other active drugs, including risperidone, clozapine, quetiapine, and haloperidol. These studies did not include olanzapine treatment arms, and no comparisons of safety or efficacy are intended between olanzapine and the other drugs mentioned. These studies may reflect different safety or efficacy data from those reflected in the prescribing information for the active agents.

This study was sponsored by Eli Lilly and Company. At the time of publication, the principal authors were employed by Lilly Research Laboratories.

Complete prescribing information for Zyprexa accompanies this reprint. Zyprexa is a registered trademark of Eli Lilly and Company.

Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285.

ORIGINAL ARTICLE

Olanzapine Treatment of Psychotic and Behavioral Symptoms in Patients With Alzheimer Disease in Nursing Care Facilities

A Double-blind, Randomized, Placebo-Controlled Trial

Jamie S. Street, MD; W. Scott Clark, PhD; Kimberley S. Gannon, PhD; Jeffrey L. Cummings, MD; Frank P. Bymaster, MSc; Roy N. Tamura, PhD; Steven J. Mitan, BSc; Deborah L. Kadam, MA; Todd M. Sanger, PhD; Peter D. Feldman, PhD; Gary D. Tollefson, MD, PhD; Alan Breier, MD; for the HGEU Study Group

Background: Patients with Alzheimer disease (AD) commonly exhibit psychosis and behavioral disturbances that impair patient functioning, create caregiver distress, and lead to institutionalization: This study was conducted to assess the efficacy and safety of olanzapine in treating psychosis and/or agitation/aggression in patients with AD.

Methods: A multicenter, double-blind, placebo-controlled, 6-week study was conducted in 206 elderly US nursing home residents with AD who exhibited psychotic and/or behavioral symptoms. Patients were randomly assigned to placebo or a fixed dose of 5, 10, or 15 mg/d of olanzapine. The primary efficacy measure was the sum of the Agitation/Aggression, Hallucinations, and Delusions items (Core Total) of the Neuropsychiatric Inventory–Nursing Home version.

Results: Low-dose olanzapine (5 and 10 mg/d) produced significant improvement compared with placebo on the Core Total (−7.6 vs −3.7 [$P<.001$] and −6.1 vs −3.7 [$P=.006$], respectively). Core Total improvement with olanzapine, 15 mg/d, was not significantly greater than placebo. The Occupational Disruptiveness score, reflecting the impact of patients' psychosis and behavioral disturbances on the caregiver, was significantly reduced in the 5-mg/d olanzapine group compared with placebo (−2.7 vs −1.5; $P=.008$). Somnolence was significantly more common among patients receiving olanzapine (25.0%-35.8%), and gait disturbance occurred in those receiving 5 or 15 mg/d (19.6% and 17.0%, respectively). No significant cognitive impairment, increase in extrapyramidal symptoms, or central anticholinergic effects were found at any olanzapine dose relative to placebo.

Conclusion: Low-dose olanzapine (5 and 10 mg/d) was significantly superior to placebo and well tolerated in treating agitation/aggression and psychosis in this population of patients with AD.

Arch Gen Psychiatry. 2000;57:968-976

From the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind (Drs Street, Clark, Gannon, Tamura, Sanger, Feldman, Tollefson, and Breier, Messrs Bymaster and Mitan, and Ms Kadam); and Departments of Neurology and Psychiatry and Biobehavioral Sciences, Reed Neurological Research Center, UCLA School of Medicine, Los Angeles, Calif (Dr Cummings). Drs Street, Clark, Tamura, Sanger, Feldman, Tollefson, and Breier, Messrs Bymaster and Mitan, and Ms Kadam are stockholders in Eli Lilly and Company, a sponsor of this study. A list of the HGEU Study Group investigators appears on page 975.

PATIENTS WITH Alzheimer disease (AD) manifest not only progressive memory impairment, cognitive deficits, and functional alterations but also a variety of neuropsychiatric disturbances (agitation, aggression, hallucinations, delusions). These symptoms ultimately affect up to 75% of individuals with dementia[1-6] and, once present, tend to be sustained or recurrent. A longitudinal assessment of 181 outpatients with AD and aggression or psychosis showed they were likely to exhibit recurrence of those symptoms during the following year (93% and 95%, respectively).[7] Jeste and Finkel[8] suggest the presumed disappearance of psychotic symptoms in patients with advanced stages of dementia could reflect an apparent, rather than real, remission because of patients' inability to articulate their delusions and hallucinations. Neuropsychiatric disturbances can affect caregivers and the overall management of the patient, including institutionalization and treatment choices. Despite the prevalence and impact of these disturbances, few studies have investigated the effect of patients' behaviors on staff at nursing care facilities. Neuropsychiatric symptoms may affect quality of patient care, increase staff supervision, and produce staff distress.[9,10]

In nursing facilities, almost 46% of residents receive psychoactive medications, including antipsychotics (17%), anxiolytics (15%), antidepressants (24%), and hypnotic agents (5%).[11] Although antipsychotics have been the treatment of choice for psychobehavioral disturbances, a meta-analytic review of 33 studies comparing conventional antipsychotics with placebo in older, severely demented patients with agitation found these agents were modestly superior to placebo.[12] A placebo-controlled dose comparison of haloperidol for psychosis and disruptive behaviors in 71 outpatients with AD revealed a positive treatment effect for the 2- to 3-mg/d dose

PATIENTS AND METHODS

STUDY GROUP

Patients were elderly nursing care facility residents, initially screened on the basis of chart reviews, staff interviews, and recommendations by the investigators and patients' family members, who met the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for possible or probable AD.[16] For study inclusion, patients must have scored 3 or higher on any of the Agitation/Aggression, Hallucinations, or Delusions items of the Neuropsychiatric Inventory–Nursing Home version (NPI/NH)[17] at screening and following a single-blind, placebo lead-in. A score of 3 or higher correlates with a clinically significant level of psychotic or behavioral symptoms, corresponding with moderate severity or frequency. Exclusion criteria included a history of a *DSM-IV*[18] Axis I disorder (eg, schizophrenia, bipolar disorder, severe or recurrent depression), any neurological condition other than AD that could contribute to psychosis or dementia, a Mini-Mental State Examination (MMSE)[19] score of greater than 24, and bedridden status. Before participation, all patients and/or their designated representative signed an informed consent document approved by the study site's institutional review board.

STUDY DESIGN

This was a 6-week, double-blind, placebo-controlled study of 206 randomized patients conducted at 28 sites, with a mean±SD enrollment of 7.4±7.2 patients per site (range, 0-29). Participants entered a 3- to 14-day, single-blind washout, placebo lead-in period. Patients who demonstrated a placebo response during the lead-in (≥50% decrease in Core Total; see "Assessments" section) were screened from the study. Patients meeting enrollment criteria were randomly allocated to 1 of 4 fixed-dose treatment groups (olanzapine, 5, 10, or 15 mg/d, or placebo) by the assignment of a unique kit number using a permuted block design at each investigational site (block size of 4). Study medication was in identical tablets and dosed once daily. Patients randomized to the 10- or 15-mg/d groups began treatment with 5 mg/d and were titrated to the target dose by 5-mg/d increments every 7 days. Patients unable to tolerate the assigned treatment were discontinued from the study.

The use of concomitant medications with primarily central nervous system activity was exclusionary, including anticholinergic agents, cholinesterase inhibitors, anticonvulsants, mood stabilizers, other antipsychotics, and tricyclic antidepressants. Benzodiazepines were allowed as rescue medication but could not exceed 4 mg/d of lorazepam equivalents for a total of 21 days during active treatment.

ASSESSMENTS

All patient assessments were conducted at the nursing facility by health care professionals, including neurologists, psychiatrists, geriatricians, psychometrists, nurses, and other medical specialists trained before study initiation. The NPI[20] evaluates psychopathology in patients with AD and other dementias. The reliability and validity of the NPI/NH have been established using nursing home patients.[17] Responses are obtained by a trained interviewer from professional caregivers involved in the ongoing care of the patient in the previous week. The NPI/NH consists of 10 behavioral and 2 neurovegetative items, with the score of each item, if present, representing the product of symptom frequency (1=occasionally to 4=very frequently) times severity (1=mild to 3=severe). For each item, an Occupational Disruptiveness score is obtained and encompasses the work, effort, time, or distress a particular behavior causes the staff caregiver (0=no disruption to 5=very severe or extreme).[17,21,22]

The primary efficacy measure consisted of the mean change from baseline to end point in the sum of the NPI/NH item scores for the core symptoms: Agitation/Aggression, Hallucinations, and Delusions (Core Total; range, 0-36). The Core Total was used to classify patients as responders

Continued on next page

group. However, 20% developed moderate-to-severe extrapyramidal symptoms (EPS). Although doses lower than 1 mg/d produced fewer EPS, they were less effective.[13]

Newer antipsychotic agents have significantly fewer adverse effects than conventional neuroleptics such as haloperidol,[14] and investigation of these newer compounds in treating behavioral symptoms of AD is warranted. Olanzapine has been shown to be effective and well tolerated in a geriatric patient population with schizophrenia.[15] To test the hypothesis that olanzapine provides safe and effective treatment for behavioral and psychotic disturbances in patients with AD, a double-blind study comparing 3 fixed doses of olanzapine to placebo was conducted among symptomatic nursing facility residents.

RESULTS

PATIENT CHARACTERISTICS AND DISPOSITION

A total of 288 patients signed informed consent, with 206 randomized and 200 providing at least 1 postbaseline data point (**Figure 1**). Two patients were screened out as placebo responders. The demographic characteristics of the 82 nonrandomized patients were similar to the 206 randomized patients. Fifty-two (43 randomized, 9 nonrandomized) discontinued use of antipsychotics, primarily because of lack of efficacy or adverse reactions, within 30 days before randomization. Patient demographics and illness characteristics were similar across treatment groups (**Table 1**). Patients had a mean age of 82.8 years; most were white (92.7%) and female (61.2%). Average time since nursing facility admission to study entry was 1.6±1.1 years; onset of AD symptoms to study entry was 4.8±4.1 years; and time from diagnosis to study entry was 2.2±1.6 years. The overall mean baseline MMSE score was 6.7±6.4. Baseline MMSE scores identified 70.9% of the study population as severely cognitively impaired (score, ≤10), 25.7% as moderately impaired (score, 11-20), and 3.4% as mildly impaired (score, 21-24). At study entry, 95.0% of patients had symptoms of agitation/aggression, 56.4% had delusions, 22.8% had hallucinations, and 57.9% had agitation/aggression and at least 1 psychotic symptom.

(≥50% reduction from baseline) and nonresponders. Secondary efficacy measures included mean changes from baseline to end point on the NPI/NH Total, Hallucinations and Delusions total (Psychosis Total), individual items, Occupational Disruptiveness score derived from the Agitation/Aggression, Hallucinations, and Delusions items (Core Disruptiveness), Brief Psychiatric Rating Scale (BPRS)[23] total and subscale, and MMSE.[19]

Three scales objectively assessed EPS: Simpson-Angus Scale,[24] Barnes Akathisia Scale,[25] and Abnormal Involuntary Movement Scale.[26] At screening, medical history taking, psychiatric assessment, physical examination, and electrocardiography (ECG) were performed. The physical examination and ECG were repeated at end point and on discontinuation following randomization. Assessment of vital signs (blood pressure, pulse, weight, temperature) and clinical laboratory testing (chemistry, electrolytes, hematology) were performed. Efficacy and safety were assessed weekly and on discontinuation.

STATISTICAL ANALYSES

A sample size of approximately 200 patients was required to achieve 80% power to detect a difference among treatment groups of at least 2.0 points in the last observation carried forward mean change on the Core Total at a 2-tailed level of $\alpha = .05$. Primary analyses were performed on an intent-to-treat basis as defined by Gillings and Koch[27] (patients with a baseline and at least 1 postbaseline measurement). Investigators with fewer than 1 patient per group for any treatment were pooled for statistical analysis.

All statistical tests were defined a priori in the protocol except the post hoc assessments of the Simpson-Angus Gait item, pooled potential anticholinergic effects, and correlations among adverse events. All tests were 2-sided, and pairwise comparisons among each of the 3 olanzapine groups and the placebo group were conducted. However, pairwise comparisons among the olanzapine groups were not systematically performed. For the primary analysis, a Bonferroni adjustment to the type I error rate for the 3 pairwise comparisons requires significance to be defined at $\alpha = .017$. For all other analyses, reported P values were unadjusted for multiple comparisons since they were exploratory, but conclusions are based on consideration of this multiplicity.

Mean change in the scores was analyzed using a last-observation-carried-forward analysis of variance (ANOVA) model that included terms for treatment, investigator (site), and treatment-by-investigator interaction. Temporal change on the Core Total used a repeated-measures analysis. This linear model included terms (considered fixed effects) for the baseline score, treatment, investigator, treatment-by-investigator interaction, visit, and treatment-by-visit interaction, and least squares means were reported. Estimates of effects were assessed by the method of restricted maximum likelihood, and an unstructured covariance matrix for the within-patient error was specified. Categorical analysis of the percentage of responders (≥50% reduction, baseline to end point) was performed using the Fisher exact test. Secondary efficacy variables were analyzed using the ANOVA model described for the primary efficacy measure.

Analyses of continuous measures of safety (laboratory analytes; ECG intervals: PR, QRS, QT, and corrected QT [QTc]; vital signs; EPS scales) were performed using last observation carried forward ANOVA models (mean changes from baseline to end point), including effects for treatment, investigator, and treatment ×investigator interaction. Categorical analyses of laboratory values, vital signs, ECG parameters, and treatment-emergent adverse events were conducted using the Fisher exact test. The proportions of patients with a Barnes Akathisia Scale score of 2 or higher at baseline and less than 2 at any postbaseline visit were compared among treatment groups by the Fisher exact test. A similar categorical analysis was conducted on the proportion of patients whose Simpson-Angus Scale score was 3 or less at baseline and increased to greater than 3 at any postbaseline visit.

Data are presented as mean±SD.

The proportion of patients completing the 6-week, double-blind therapy was 76.6% in the placebo group and 80.4%, 72.0%, and 66.0% in the 5-, 10-, and 15-mg/d olanzapine groups, respectively. Use of lorazepam equivalents (mean [SD] daily dose, 0.4±0.5 mg/d) among patients taking benzodiazepines (46.1%, 95/206) was not significantly different in the 4 treatment groups. No significant differences were seen between completers and noncompleters regarding characteristics or baseline scores except NPI/NH Apathy and BPRS Negative Symptoms subscale, which were significantly worse among noncompleters (2.38±3.34 vs 3.88±4.94 [$t_1 = 2.39$, $P = .02$] and 4.09±3.53 vs 6.50±5.41 [$t_1 = 3.35$, $P < .001$], respectively).

EFFICACY RESULTS

On the Core Total, the 5- and 10-mg/d olanzapine groups experienced significantly greater improvement than the placebo group (**Table 2**). Patients receiving 5 mg/d improved by 7.6±7.7 points (placebo improvement, 3.7±10.3; $t_1 = 3.65$, $P < .001$), while patients receiving 10 mg/d improved by 6.1±8.2 points ($t_1 = 2.80$, $P = .006$). The 15-mg/d group was not statistically superior to placebo (olanzapine, 15 mg/d, mean change, −4.9±7.8; $t_1 = 1.17$, $P = .24$). The proportion of patients exhibiting a response on the Core Total (≥50% reduction, baseline to end point) was significantly greater for the 5-mg/d (65.5%, 36/55; Fisher exact $P = .005$) and 10-mg/d (57.1%, 28/49; Fisher exact $P = .04$) olanzapine groups compared with placebo (35.6%, 16/45) but not for the 15-mg/d group (43.1%, 22/51; Fisher exact $P = .53$).

Visitwise analysis of the Core Total (**Figure 2**) showed a statistically significant treatment effect relative to placebo at week 2 for the 5-mg/d (−4.1±7.6 vs −1.6±7.7; $t_1 = 2.64$, $P = .009$) and 10-mg/d (−3.6±6.4 vs −1.6±7.7; $t_1 = 2.40$, $P = .02$) olanzapine groups. The 5-mg/d olanzapine group continued to improve significantly for the remainder of the 6-week study period. The 10-mg/d group showed increasing improvement significantly superior to placebo at weeks 2, 4, 5, and 6. The 15-mg/d group showed an improvement throughout the entire treatment period that was not significantly greater than placebo. Patients treated with 5 mg/d of olanzapine dem-

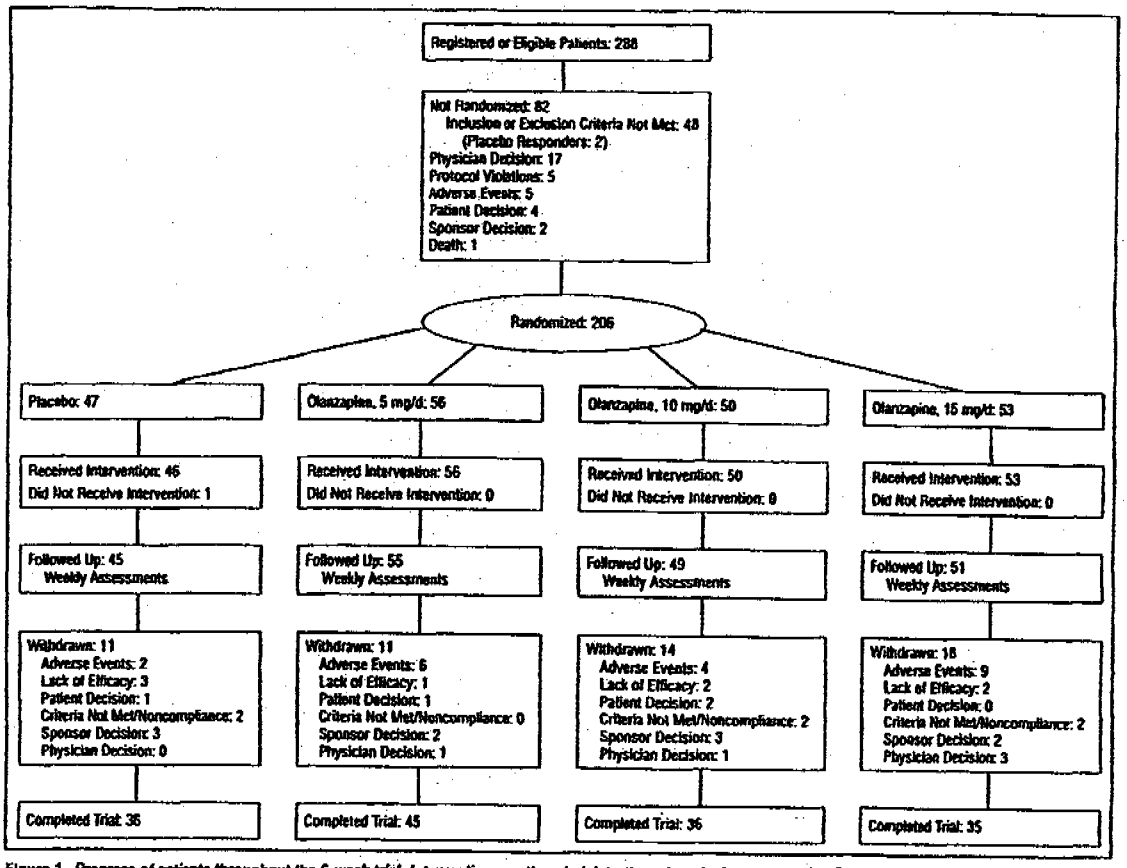

Figure 1. *Progress of patients throughout the 6-week trial. Intervention was the administration of study drug or placebo. Following randomization, 1 patient (placebo group) did not receive study drug but was included in the intent-to-treat efficacy analyses. Patients were included in the analyses of change from baseline to end point if they had both a baseline score and at least 1 postbaseline score. Following randomization and intervention, 6 patients were excluded from efficacy analyses for the following reasons: no postbaseline score for the primary efficacy measure (n=2) and improperly administered Neuropsychiatric Inventory–Nursing Home version (n=4). A total of 200 patients were included in the primary efficacy analysis.*

onstrated significantly greater improvement relative to placebo on nearly all secondary efficacy measures, while the 10-mg/d group demonstrated significant improvement on several measures (Table 2). The 5- and 10-mg/d olanzapine groups each had significantly greater mean score reductions compared with placebo on the Agitation/Aggression item (−4.1±3.7 vs −2.1±4.6, [t_1=2.50, P=.01] and −3.9±4.2 vs −2.1±4.6 [t_1=2.39, P=.02], respectively) and the Psychosis Total (Hallucinations and Delusions total) (−3.6±5.6 vs −1.6±7.3 [t_1=3.27, P=.001] and −2.2±5.8 vs −1.6±7.3 [t_1=2.11, P=.04], respectively).

Improvement in noncognitive neuropsychiatric symptoms associated with olanzapine treatment had a positive impact on nursing facility caregivers. A statistically significant reduction in caregiver distress, measured by the sum of the Occupational Disruptiveness scores for Agitation/Aggression, Hallucinations, and Delusions (Core Disruptiveness) was seen for patients treated with 5 mg/d of olanzapine (−2.7±3.2 vs −1.5±3.5; t_1=2.69, P=.008). Caregivers of patients treated with 5 mg/d of olanzapine also had similar reductions in Occupational Disruptiveness associated with Anxiety, Appetite and Eating Disorders, Delusions, Depression/Dysphoria, and

Table 1. Baseline Patient Characteristics*

Characteristic	Placebo	Olanzapine, 5 mg/d	Olanzapine, 10 mg/d	Olanzapine, 15 mg/d
No. of patients	47	56	50	53
Age, y				
Mean (SD)	81.4 (6.7)	82.9 (6.5)	83.6 (6.5)	83.0 (6.7)
Range	61-94	67-94	66-97	67-94
Sex, No. (%)				
Male	18 (38.3)	23 (41.1)	17 (34.0)	22 (41.5)
Female	29 (61.7)	33 (58.9)	33 (66.0)	31 (58.5)
Time from nursing home admission to visit 1, y				
Mean (SD)	1.6 (1.5)	1.5 (1.2)	1.6 (1.6)	1.7 (1.7)
Time from first AD symptom to visit 1, y				
Mean (SD)	4.5 (2.9)	4.3 (3.1)	5.2 (5.0)	5.0 (3.7)
Time from AD diagnosis to visit 1, mean (SD), y	2.2 (2.1)	1.6 (1.5)	2.7 (2.8)	2.4 (2.4)
MMSE baseline score, mean (SD)	7.3 (6.3)	7.3 (6.5)	6.6 (6.7)	6.4 (6.7)

*No statistically significant differences were found among treatment groups. AD indicates Alzheimer disease; MMSE, Mini-Mental State Examination.

Table 2. Summary of Efficacy Results*

Measurement Scale	n	Baseline, Mean (SD)	Change, Mean (SD)†	Test Statistic (*df*)	*P* (vs Placebo)‡
NPI/NH Core Total§					
Placebo	45	14.8 (8.7)	−3.7 (10.3)	...	...
Olanzapine, mg/d					
5	55	14.4 (7.4)	−7.6 (7.7)	3.65 (1)	<.001
10	49	14.1 (7.4)	−6.1 (8.2)	2.80 (1)	.006
15	51	14.1 (7.5)	−4.9 (7.8)	1.17 (1)	.24
NPI/NH Occupational Disruptiveness‖					
Placebo	45	5.3 (3.4)	−1.5 (3.5)	...	...
Olanzapine, mg/d					
5	55	5.1 (3.3)	−2.7 (3.2)	2.69 (1)	.008
10	49	5.0 (2.9)	−2.1 (2.7)	1.08 (1)	.28
15	51	5.7 (3.3)	−2.3 (3.4)	1.47 (1)	.14
NPI/NH Agitation/Aggression					
Placebo	45	7.4 (3.4)	−2.1 (4.6)	...	...
Olanzapine, mg/d					
5	55	8.4 (3.2)	−4.1 (3.7)	2.50 (1)	.01
10	49	8.4 (3.0)	−3.9 (4.2)	2.39 (1)	.02
15	52	7.9 (3.4)	−3.1 (4.1)	0.53 (1)	.60
NPI/NH Psychosis Total¶					
Placebo	45	7.4 (7.3)	−1.6 (7.3)	...	...
Olanzapine, mg/d					
5	55	6.2 (6.3)	−3.6 (5.6)	3.27 (1)	.001
10	49	5.8 (5.7)	−2.2 (5.8)	2.11 (1)	.04
15	51	6.2 (6.4)	−1.9 (5.3)	1.28 (1)	.20
NPI/NH Hallucinations					
Placebo	45	2.4 (3.7)	0.0 (4.2)	...	...
Olanzapine, mg/d					
5	55	1.7 (3.2)	−0.7 (3.2)	2.74 (1)	.007
10	49	1.3 (3.0)	−0.2 (3.1)	2.00 (1)	.05
15	51	2.2 (3.8)	−0.7 (2.9)	1.66 (1)	.10
NPI/NH Delusions					
Placebo	45	4.9 (4.7)	−1.6 (4.3)	...	...
Olanzapine, mg/d					
5	55	4.5 (4.3)	−2.9 (3.9)	2.52 (1)	.01
10	49	4.4 (4.4)	−2.0 (4.2)	1.45 (1)	.15
15	52	4.0 (4.0)	−1.3 (3.3)	0.47 (1)	.64
NPI/NH Depression/Dysphoria					
Placebo	45	2.6 (3.4)	−1.0 (3.2)	...	...
Olanzapine, mg/d					
5	55	2.8 (3.7)	−2.0 (3.7)	1.08 (1)	.28
10	49	2.1 (3.1)	−0.6 (3.1)	0.00 (1)	>.99
15	51	2.2 (3.0)	−0.2 (3.8)	0.99 (1)	.32
NPI/NH Total					
Placebo	45	44.2 (24.3)	−10.4 (27.5)	...	...
Olanzapine, mg/d					
5	55	43.7 (23.0)	−18.7 (21.3)	2.89 (1)	.005
10	49	40.7 (20.8)	−14.0 (21.7)	1.72 (1)	.09
15	51	41.0 (22.0)	−9.7 (26.1)	0.22 (1)	.83
BPRS Total					
Placebo	33	25.7 (8.4)	−1.4 (11.1)	...	...
Olanzapine, mg/d					
5	40	30.9 (11.7)	−6.8 (8.5)	2.88 (1)	.005
10	37	26.0 (11.0)	−5.6 (10.0)	1.87 (1)	.06
15	39	30.0 (10.9)	−4.0 (10.9)	1.52 (1)	.13
BPRS Positive subscale#					
Placebo	35	7.7 (3.2)	−0.4 (4.4)	...	...
Olanzapine, mg/d					
5	40	8.5 (4.6)	−2.0 (3.5)	1.93 (1)	.05
10	37	7.4 (3.9)	−1.4 (3.5)	0.84 (1)	.40
15	41	8.1 (4.9)	−1.4 (5.2)	1.44 (1)	.15
BPRS Anxiety/Depression subscale**					
Placebo	35	3.8 (3.2)	0.1 (3.6)	...	...
Olanzapine, mg/d					
5	42	5.0 (3.0)	−1.3 (3.0)	2.05 (1)	.04
10	39	4.2 (3.0)	−1.5 (2.5)	2.30 (1)	.02
15	39	4.2 (3.3)	−0.6 (2.7)	1.07 (1)	.29

**NPI/NH indicates Neuropsychiatric Inventory–Nursing Home version; BPRS, Brief Psychiatric Rating Scale; and ellipses, not applicable.*
†Mean change (SD) from baseline to end point, last observation carried forward.
‡P values for pairwise comparisons to placebo were calculated by analysis of variance.
§Sum of NPI/NH Agitation/Aggression, Hallucinations, and Delusions item scores.
‖Occupational Disruptiveness of caregivers for the NPI/NH items of Agitation/Aggression, Hallucinations, and Delusions.
¶Sum of NPI/NH Hallucinations and Delusions items scores.
#Consists of Conceptual Disorganization, Suspiciousness, Hallucinatory Behavior, and Conceptual Thought Disorder.
***Consists of Somatic Concern, Anxiety, Guilt Feelings, and Depressive Mood.*

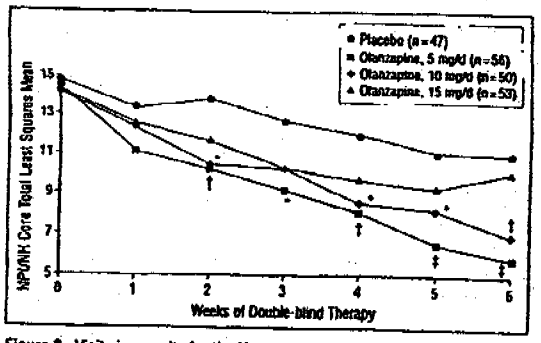

Figure 2. *Visitwise results for the Neuropsychiatric Inventory–Nursing Home version (NPI/NH) Core Total score. The NPI/NH Core Total (sum of the Agitation/Aggression, Hallucinations, and Delusions items) scores across the 6-week study period for placebo and olanzapine groups (5, 10, and 15 mg/d). Patients treated with 5 mg/d of olanzapine showed a significantly greater improvement compared with placebo at week 2, which was maintained throughout the study. Patients treated with 10 mg/d of olanzapine showed a significantly greater improvement at week 2, which was maintained at weeks 4 to 6. Asterisk indicates P<.05 vs placebo; dagger, P<.01 vs placebo; and double dagger, P<.001 vs placebo.*

Hallucinations items. Although the reduction in Occupational Disruptiveness for the 10-mg/d olanzapine group did not differ significantly from placebo, it also did not differ significantly from the 5-mg/d group.

Significantly greater improvement associated with 5 mg/d of olanzapine was evident in the BPRS Total (−6.8±8.6 vs −1.4±11.1; t_1=2.88, P=.005). The 5- and 10-mg/d olanzapine groups exhibited significantly greater improvement on the BPRS Anxiety/Depression subscale relative to placebo (−1.3±3.0 vs +0.1±3.6 [t_1=2.05, P=.04] and −1.5±2.5 vs +0.1±3.6 [t_1=2.30, P=.02], respectively). Changes in NPI/NH Depression/Dysphoria scores were not significantly different among any of the treatment groups; mean scores were low at baseline, and fewer than one third of patients experienced mood alterations. The MMSE scores of patients in the 3 olanzapine groups were not significantly different from baseline (mean change, 5 mg/d: 0.8±3.9; 10 mg/d: −0.5±3.3; 15 mg/d: −1.0±3.1) or from placebo (mean change, −0.3±2.2).

SAFETY RESULTS

There were no statistically significant mean changes in EPS, as measured by the Simpson-Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale, or in the categorical analysis of treatment-emergent adverse events. The incidence of spontaneously reported EPS was low among the olanzapine groups: no EPS event (tremor, hypertonia, cogwheel rigidity, hyperkinesia, akathisia, dyskinesia, dystonia, extrapyramidal syndrome [parkinsonism], tardive dyskinesia) was statistically different from placebo.

Treatment-emergent adverse events represent signs and symptoms spontaneously identified clinically during the study and do not reflect formalized, objective, operationalized data collected by the efficacy measures. All olanzapine-emergent events were similar compared with placebo except somnolence and abnormal gait (**Table 3**). The olanzapine groups had significantly higher rates of somnolence than the placebo group, with 4 patients discontinuing due to somnolence (olanzapine, 5 mg/d: 1; 10 mg/d: 0; 15 mg/d: 3). The risk of somnolence in the 5-, 10-, and 15-mg/d olanzapine groups was estimated to be 4.9, 5.2, and 8.2 times greater than in the placebo group, respectively. Within the olanzapine groups, 28.3% of patients who experienced somnolence also had abnormal gait, compared with 12.4% of patients without somnolence (Fisher exact P=.02). Results of an analysis of covariance controlling for somnolence showed no significant effect of somnolence on the primary efficacy results, and the treatment effects remained statistically significant. Treatment-emergent weight changes were not significantly greater than placebo for olanzapine. Weight loss occurred at an incidence of 10% or more (Table 3), whereas weight gain was 10% or less (placebo: 3 [6.4%]; olanzapine, 5 mg/d: 3 [5.4%]; olanzapine, 10 mg/d: 1 [2.0%]; olanzapine, 15 mg/d: 0 [0.0%]).

Table 3. Treatment-Emergent Adverse Events*

COSTART Term	Placebo (n = 47)	Olanzapine 5 mg/d (n = 56)	Olanzapine 10 mg/d (n = 50)	Olanzapine 15 mg/d (n = 53)
Accidental injury†	13 (27.7)	14 (25.0)	12 (24.0)	20 (37.7)
Somnolence	3 (6.4)	14 (25.0)‡	13 (26.0)‡	19 (35.8)‖
Pain	5 (10.6)	8 (14.3)	6 (12.0)	13 (24.5)
Abnormal gait	1 (2.1)	11 (19.6)§	7 (14.0)	9 (17.0)‡
Anorexia	4 (8.5)	1 (1.8)	2 (4.0)	8 (15.1)
Ecchymosis	7 (14.9)	5 (8.9)	6 (12.0)	8 (15.1)
Fever	1 (2.1)	5 (8.9)	7 (14.0)	7 (13.2)
Agitation	4 (8.5)	5 (8.9)	6 (12.0)	6 (11.3)
Weight loss	3 (6.4)	0 (0.0)	2 (4.0)	6 (11.3)
Cough increased	3 (6.4)	7 (12.5)	5 (10.0)	4 (7.5)
Peripheral edema	3 (6.4)	2 (3.6)	6 (12.0)	4 (7.5)
Nervousness	2 (4.3)	4 (7.1)	6 (12.0)	1 (1.9)

**Data are presented as number (percentage) and include all treatment-emergent adverse events with an incidence ≥ 10% or significantly greater than placebo, regardless of cause. No statistically significant differences occurred among treatment groups. COSTART indicates Coding Symbols for a Thesaurus for Adverse Reaction Terms.*

†Accidental injury includes abrasion, bruise, cut or laceration, fall, fracture, and skin tear.

‡P<.05, relative to placebo (Fisher exact test).

§P<.01, relative to placebo (Fisher exact test).

‖P<.001, relative to placebo (Fisher exact test).

Patients treated with 5 or 15 mg/d of olanzapine had significantly higher rates of treatment-emergent abnormal gait (stooped posture, unsteady gait, leaning, ambulation dysfunction) than placebo-treated patients. The risk of abnormal gait in the 5-, 10-, and 15-mg/d olanzapine groups was estimated to be 11.2, 7.5, and 9.4 times greater than in the placebo group, respectively. Of the 28 patients reported to have treatment-emergent abnormal gait, 24 had Simpson-Angus Scale assessments. Of those 24 patients, the Gait item score worsened from baseline to end point for 7 patients (placebo: 1; olanzapine, 5 mg/d: 1; olanzapine, 10 mg/d: 1; olanzapine, 15 mg/d: 4). Post hoc analysis of the Simpson-Angus Gait item revealed no statistically significant differences for any olanzapine group compared with placebo in mean change from baseline to end point.

Anticholinergic effects were assessed by identifying reported classification terms from the Coding

Symbols for a Thesaurus fo. ..dverse Reaction Terms (COSTART) that potentially could be related to central or peripheral anticholinergic activity. (Central activity terms included *agitation, confusion, delirium, delusions, dyskinesia, fever, hallucinations, thinking abnormal*, and *twitching*. Peripheral activity terms included *amblyopia, constipation, dry mouth, dry skin, fecal impaction, fever, intestinal obstruction, tachycardia, urinary retention*, and *vasodilation*.) There were no significant differences in any olanzapine group for any of the individually listed central or peripheral COSTART terms compared with placebo. Pooling COSTART peripheral anticholinergic terms revealed a significant difference between the 15-mg/d olanzapine group and placebo (26.0% and 6.4%, respectively; Fisher exact $P=.008$). No significant differences were evident when central anticholinergic terms were pooled.

No clinically significant differences emerged between placebo and olanzapine groups for changes in vital signs, weight, or ECG measures. The incidence of clinically meaningful orthostatic hypotension (≥30 mm Hg decrease of systolic blood pressure, supine to sitting) was nearly identical for placebo patients (7.0%) and olanzapine patients (7.2%, Fisher exact $P>.99$). The effect of olanzapine on cardiac function was addressed in the analyses of mean change from baseline to end point and categorical changes for ECG heart rate and interval times (PR, QRS, QT, QTc). There were no statistically significant differences between any of the olanzapine groups and placebo.

COMMENT

In the present study, low-dose olanzapine (5 and 10 mg/d) was significantly superior to placebo and safe in treating behavioral and psychotic symptoms of patients with AD in nursing care facilities. Patients receiving these lower doses showed an approximate 50% mean improvement in NPI/NH Core Total scores, as identified by their caregivers, with clinical improvements corresponding to an average change from moderate severity or frequent symptoms to mild or infrequent. This is one of only a few controlled clinical trials demonstrating the efficacy and safety of atypical antipsychotics for behavioral and psychotic disturbances in elderly patients.

Two placebo-controlled, double-blind studies have been reported using the atypical antipsychotic risperidone. De Deyn et al[28] compared placebo and flexible-dose (0.5-4 mg/d) risperidone or haloperidol for behavioral symptoms. The percentage of risperidone-treated (mean dose, 1.1 mg/d) and haloperidol-treated (mean dose, 1.2 mg/d) patients demonstrating clinical improvement (≥30% reduction from baseline to end point in BEHAVE-AD Total) was not significantly greater than placebo. Aggression scores were significantly improved relative to placebo for risperidone, and EPS were significantly higher in patients receiving haloperidol than risperidone or placebo. Katz et al[29] reported a large, placebo-controlled study of flexible-dose risperidone (0.5-2.0 mg/d) for psychotic and behavioral symptoms. Doses of 1 or 2 mg/d were effective in reducing delusions and aggressiveness; the higher dose was associated with a greater incidence of EPS, somnolence, and peripheral edema.

To date, th ave been no published placebo-controlled studies of quetiapine or clozapine in elderly demented patients. Clozapine, in small, open-label studies and retrospective case examinations, was reported effective for various psychotic disease states.[30-32] Confusion, sedation, and a higher risk of agranulocytosis in older patients were noted.[33,34] Interim analysis of an open-label trial of quetiapine fumarate in elderly patients suggested an improvement in the BPRS Total and Clinical Global Impressions of Severity of Illness scores.[35]

In this study of olanzapine, the lowest dose (5 mg/d) appeared to have the greatest effect. Other atypical and conventional antipsychotics also are optimal at lower doses in elderly demented patients, usually due to decreased tolerability at higher doses (EPS, orthostatic hypotension, confusion).[13,28,29,36] This is the first controlled study of an antipsychotic in an elderly demented population using a dose (15 mg/d) that is effective and tolerated in other psychotic disorders.[14,37,38]

The inverse correlation of efficacy and olanzapine dose is potentially multifactorial. Age-related pharmacokinetic changes (absorption, distribution, metabolism, excretion of drugs)[39] and age-related (particularly >70 years)[40] pharmacodynamic alterations (end-organ receptor density and affinity, postreceptor response) influence dose and tolerability.[41,42] These, coupled with the ongoing neuropathology of AD,[43] potentially contributed to the decreased drug response seen with the high dose in the present study.[42,44] The 15-mg/d dose of olanzapine demonstrated a negative effect on tolerability and potentially affected efficacy.

Because of the reduction in cholinergic neurotransmission in AD, drugs with moderate-to-significant anticholinergic potential are avoided or used with caution.[45] Although the incidence of pooled anticholinergic peripheral effects was higher with 15 mg/d of olanzapine relative to placebo, central effects were not significantly different, including cognition. The MMSE scores in all 3 olanzapine groups were not significantly different from baseline or placebo. Olanzapine demonstrates a relatively high affinity for muscarinic receptors in preclinical in vitro binding assays using low-ionic-strength buffer.[46] However, in physiological binding medium, the affinity of olanzapine, but not atropine, was greatly reduced.[47] These latter data correlate with both ex vivo and in vivo studies that demonstrate that olanzapine has relatively minimal functional effects at muscarinic receptors.[48-51]

Olanzapine was generally well tolerated in this elderly population. Somnolence was dose related in the olanzapine treatment groups, and abnormal gait occurred at a statistically significantly higher incidence compared with placebo in the 5- and 15-mg/d groups. These data are of clinical significance in an elderly patient population potentially at risk for these events. Cardiovascular monitoring demonstrated no clinically significant effects, with no increases in incidence of orthostatic hypotension, arrhythmias, or QTc prolongation in any of the olanzapine groups compared with placebo. Objective EPS were absent with olanzapine use. This is particularly important because EPS occur with a higher incidence in geriatric patients with dementia, even in those previously unexposed to antipsychotics.[52,53]

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Neuropsychiatric symptoms may have substantial impact on caregiver job satisfaction, and nursing facilities may have difficulty attracting and retaining caregiver staff. The beneficial effect of olanzapine, 5 mg/d, on Occupational Disruptiveness reflecting Core Disruptiveness (Agitation/Aggression, Hallucinations, and Delusions) and other behavioral items was significant.

Limitations of the present study include a duration too short to assess potential long-term antipsychotic effects, such as tardive dyskinesia. The study was not powered to detect infrequent adverse events between treatment groups or to stratify the results on sex or age, and the fixed dosing does not mirror clinical practice. Additional studies are needed to determine the benefit of olanzapine to noninstitutionalized patients, the long-term effects of treatment, the comparative safety and efficacy compared with other agents used in patients with AD, and the impact on quality-of-life scales and health economics.

In summary, this study indicates that low-dose olanzapine (5 and 10 mg/d) is effective in reducing behavioral disturbances and psychotic symptoms in patients with AD residing in nursing care facilities. The safety profile of low-dose olanzapine indicated it was well tolerated relative to placebo, including no significant cognitive decline during the 6 weeks of therapy.

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